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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/117,218	01/11/99	BROWN S	117-261

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EXAMINER	
NGUYEN, Q	
ART UNIT	**PAPER NUMBER**
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/117,218	Applicant(s) BROWN ET AL.	
	Examiner Quang Nguyen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed 15 December 2000 in paper no. 11 has been entered.

New claims 13-22 are examined on the merits herein.

Response to Amendment

The rejection of claim 11 under 35 USC § 102(a) in view of Randazzo et al. is withdrawn in light of Applicant's submission of the Declaration.

The rejection of claim 10 under 35 USC § 112, First Paragraph for Written Description is withdrawn in light of Applicant's submission of a document indicating that Strain 1716 has been deposited under the provisions of the Budapest Treaty.

At the request of Applicant, the provisional rejection of pending claims in the present application as being obvious over claims of the co-pending Application No. 08/776,350 is held in abeyance until an indication of allowable claims is made.

Upon further careful consideration of the present application, following is the new ground of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing non-neuronal tumor cells in a mammal, which method comprises the step of intratumoral injection of an effective amount of a mutant herpes simplex virus whose genome has been modified in the γ34.5 such that the gene is non-functional, and wherein the mutant virus infects, replicates and lyses non-neuronal tumor cells in the mammal and thereby said non-neuronal tumor cells are killed, does not reasonably provide enablement for other embodiments in the pending claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a non-neuronal cancer in a mammal, which method comprises the steps of administering to the mammal an effective amount of a mutant herpes simplex virus which has been modified in the γ34.5 gene such that the gene is nonfunctional; and achieving infection and replication of the virus and lysis of a non-neuronal tumor cell in the mammal by the virus, thereby treating the non-neuronal cancer.

The specification discloses various deletion and point mutants in the RL1 gene coding for the ICP 34.5 protein (or gamma 34.5 gene) for both HSV-1 strain 17 and HSV-2 strain HG52, including, HSV-1 strains 1716, 1771 and HSV-2 strains 2604, 2616, 2621. The specification teaches that HSV-1716 mutant replicates efficiently *in vitro* in both human malignant mesothelioma cell line REN and melanoma cell line 1205. HSV-1716 mutant has also been shown to lyse REN cells and I-45 cells (another

human mesothelioma cell line) effectively *in vitro*. Using a model of human malignant mesothelioma growing in the peritoneal cavity of SCID mice, and SCID mice with pre-formed intracutaneous 1205 tumors, the specification discloses that administration of HSV-1716 mutant into tumor-bearing mice resulted in a decrease in tumor mass and an improvement in survival. The specification further teaches that the HSV-1716 mutant is replication restricted to tumor cells causing oncolytic activity, and that it does not disseminate or persist in treated mice.

The above evidence has been noted and considered. However, the evidence can not be extrapolated to the claimed method of treating a non-neuronal cancer in a mammal which encompasses any and all routes of administering an effective amount of a mutant herpes simplex virus whose genome has been modified in the γ34.5 gene such that the gene is non-functional into said mammal. The specification is not enabled for such a broadly claimed invention for reasons already stated in the previous Office Action mailed on 08/15/2000 in paper no. 10 (see pages 6 and 7). Essentially, the instant specification fails to provide sufficient guidance demonstrating that effective amounts of the mutant herpes simplex virus can be delivered to non-neuronal cancer cells by any and all routes of delivery in a mammal with a competent immune system, such that effective killing of non-neuronal cancer cells occurs and thereby treating the non-neuronal cancer. As stated in the previous Office action, viral vector targeting *in vivo* to desired tissues or organs, for this instance non-neuronal cancer cells, continues to be unpredictable and inefficient, and at the effective filing date of the present application the resolution to vector targeting had not been achieved in the art as

exemplified at least by the teachings of Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998, Cited previously) and Verma et al. (Nature 389:239-242, 1997, Cited previously). Additionally, Verma et al. discussed the role of the host immune system in inhibiting the efficient targeting of viral vectors, in this instance the mutant herpes simplex virus, to targeted cells or tissues. Thus, there is a need for administering higher concentrations of the mutant herpes simplex virus into a patient than one may desire so that effective amount of the virus could be achieved in non-neuronal tumor cells. However, it is clear from the teachings of Martuzar et al. (U.S. Patent No. 6,139,834) that herpes simplex virus has a very broad host range and seems capable of infecting all cell types in the CNS (column 7, lines 7-11). In order to avoid any deleterious effects from high concentration applications of the mutant herpes simplex virus, the virus still needs to be targeted specifically to the tumor cells. The instant specification fails to teach one of skilled in the art how to overcome the unpredictability and inefficiency of *in vivo* viral vector targeting known in the art, such that an effective amount of the mutant herpes simplex virus can be delivered to non-neuronal tumor cells by any and all modes of delivery to cause effective oncolysis. It is unclear whether the success obtained in the SCID mouse (without a functional immune system) model of human mesothelioma via intraperitoneal injection of the mutant herpes simplex virus can be similarly achieved for the situation of a mammal having non-neuronal cancers in a competent immune system. Additionally, regarding to clinical relevance of animal models, Vieweg & Gilboa (Cancer Invest. 13:193-201, 1995) stated that "Many important concepts concerning human cancers have been derived from initial studies utilizing appropriate animal

models. They are providing valuable information that may or may not work when applied to a clinical setting." (column 2, last paragraph, page 195). Vieweg & Gilboa further stated that "appropriate animal models should be based on the choice of a highly relevant animal tumor model that corresponds in its origin and tumor biology with a particular form of human cancer as well as on orthotopic implantation of the tumor cells into their organ of origin" (column 1, second paragraph, page 196). Finally, the problems that were encountered in a recent phase II trial of ovarian BRCA1 gene therapy using a recombinant retrovirus being delivered through an intraperitoneal injection illustrated some of the issues raised above (Tait et al., Clin Cancer Res. 5:1708-1714, 1999). Results from that study showed that the recombinant retrovirus was rapidly degraded upon infusion patients with ovarian cancers, and the patients developed quickly neutralizing antibodies against the amphoteric retroviral envelope. The trial study was terminated when none of the treated patients showed any response. Despite using the same vector and the same infusion protocol, the failure of the BRCA1 gene therapy in phase II has been attributed to unanticipated factors such as, the tumor load burden and immune system status of the treated patient population (See abstract).

Accordingly, due to the lack of guidance or direction provided by the specification, the unpredictability of the *in vivo* viral vector targeting art, and the breadth of the claims, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and use the broadly claimed invention.

In response to the previous Office Action regarding to the mode of administration of the virus in the claimed method of treatment, Applicants argued that there was no reason to believe that alternative methods other than the intraturmoral injection mode, would not have also been suitable in the claimed treatment method. The examiner respectfully finds the argument to be unpersuasive because it does not address the concerns raised above. Therefore, claims 13-22 remain rejected under 35 USC § 112, First Paragraph for the reasons set forth in the preceding paragraphs.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 13 and its dependent claims, the phrase "achieving infection and replication .....by the virus" is unclear because the virus can not take an active step of achieving infection and replication and lysis by itself without the administration step to the mammal. To overcome this rejection, it is suggested that the phrase - - wherein the virus infects, replicates and lyses said non-neuronal tumor cell in the mammal, thereby treating the non-neuronal cancer- - is used instead.

In claims 14-22, the article "a" in each claim renders the claims indefinite because which method of claim 13 do these claims refer to? It is noted that because of the opening language of the term "comprising", claim 13 contains a number of methods

having many different steps. It is suggested that "a" should be replaced with - - the - - to overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 13-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994).

The claims are drawn to a method of treating a non-neuronal cancer in a mammal, preferably a human, which method comprises the steps of administering to the mammal an effective amount of a mutant herpes simplex virus which has been modified in the γ34.5 gene such that the gene is non-functional, and achieving infection and replication of the virus and lysis of a non-neuronal tumor cell in the mammal by the virus, thereby treating the non-neuronal cancer; the same method wherein said cancer is a primary or a metastatic tumor; or wherein the cancer is a mesothelioma, ovarian carcinoma, bladder cancer or melanoma; or wherein the mutant herpes simplex virus is a type I herpes simplex virus; or wherein the mutant herpes simplex virus has been modified within the BamH1 restriction fragment of the long terminal repeat of the viral

genome, preferably the modification is a deletion of from 0.1 to 3 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome.

With respect to a method for killing tumor cells in a subject via intratumoral injection of mutant herpes simplex virus, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67). Therefore, Martuza et al. clearly anticipate the instantly claimed invention.

It should be noted that the U.S. Patent No. 6,139,834 of Martuza et al. has an effective filing date of June 23, 1994 because of the supports found in column 3, lines 52-58; column 12, lines 6-7; column 15, lines 41-50 and other embodiments contained in the U.S. Patent No. 5,585,096 of Martuza et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994) in view of either MacLean et al. (J. Gen. Virol. 72:631-639, 1991, Cited

previously) or Brown et al. (WO 92/13943 with a publication date of August 20, 1992; PTO-1449, IDS) and Markert et al. (Neurosurgery 32:597-603, 1993; IDS).

The claims are drawn to a method of treating a non-neuronal cancer in a mammal, preferably a human, which method comprises the steps of administering to the mammal an effective amount of a mutant herpes simplex virus which has been modified in the γ34.5 gene such that the gene is non-functional, and achieving infection and replication of the virus and lysis of a non-neuronal tumor cell in the mammal by the virus, thereby treating the non-neuronal cancer; the same method wherein the mutant herpes simplex virus has been modified within the BamH1 restriction fragment of the long terminal repeat of the viral genome, preferably the modification is a deletion of from 0.1 to 3 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome, more preferably the deletion is from 0.7 to 0.8 kb; and the same method wherein the mutant herpes simplex virus is strain 1716.

With respect to a method for killing tumor cells in a subject via intratumoral injection of mutant herpes simplex virus, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly

claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67). Martuza et al. do not teach a method of killing tumor cells in a subject using the mutant herpes simplex virus wherein there is a deletion from 0.7 to 0.8 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome, or wherein the mutant herpes simplex virus is strain 1716.

Both MacLean et al. and Brown et al. disclose HSV-1 mutant 1716 and they both teach that strain 1716 contains a 759 bp deletion in the γ34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See abstract and Fig. 3 on page 634 of MacLean et al.; page 4, lines 16-31 in Brown et al.). The deletion is associated with the non-neurovirulence for strain 1716 comparing to the parental wild type strain.

Markert et al. teach a herpes simplex virus-1 called R3616 with decreased neurovirulence (See abstract) and the virus contains a 1kb deletion in the γ34.5 gene

(page 598, column 1, bottom of third paragraph). Markert et al. further teach that R3616 possesses antineoplastic effects and it significantly prolonged average survival without producing premature encephalitic deaths in a nude mouse intracranial glioma model (See abstract).

Accordingly, it would have been obvious to one of ordinary skilled in the art at the time of invention was made to substitute any of the mutant herpes simplex virus utilized in the method disclosed by Martuza et al. with mutant virus strain 1716 taught by MacLean et al. and Brown et al., and one of ordinary skilled in the art would have expected to successfully killing tumor cells in a subject via an intratumoral route of delivery. This is because it was well known in the art that mutant herpes simplex virus having a deletion in the γ34.5 gene has reduced non-neurovirulence and still possesses anti-neoplastic effects as exemplified by the teachings of Markert et al. and Martuza et al. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Deborah Crouch, Ph.D., may be reached at (703) 308-1126, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.

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